Original Article

Role of Heparin in Arterial Line Flushing Solution on Platelet Count and Indwelling Arterial Catheter Patency after Cardiac Valvular Surgery

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Abstract:

Background: Heparin can cause thrombocytopenia but what is it's effect on platelet when used in solution for flushing indwelling arterial catheter is not clear. This study was designed to find out any effect of heparin on platelet count and to see the efficacy of normal solution as flushing solution.

Method:This was a prospective randomized comparative clinical trial in the Department of Cardiovascular Surgery of National Institute of Cardiovascular Diseases Hospital, Sher - e - Banglanagar, Dhaka,Bangladesh during the period from july 2016 to june 2017. Total sixty patients who underwent single valve replacement surgery were divided into two groups and were evaluated for heparin effect and compared for arterial catheter patency rate.

Results: Platelet count on third postoperative day is 226517+- 60185/ml and 245957+-52826/ml in heparinized flush solution and normal saline flush solution group respectively. The difference of mean is not significant with p value 0.188. Arterial catheter patency rate was 50.0% in heparinized flush solution group and 43.3% in normal saline flush solution group on third postoperative day which signifies no difference between the groups with p value 0.607.

Conclusion: The use of heparin in normal saline in continuous flushing devices for an arterial catheter does not significantly reduce platelet counts in cardiac valve surgery patients in comparison to normal saline. It seems that there is no difference in the use of heparinized and normal saline solutions to maintain indwelling arterial catheter patent.

Key words: Heparin, Platelets, Cardiac Surgical Procedures.

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Introduction:

Heparinized saline solution is used to prevent occlusion in the arterial catheters and central venous pressure monitoring catheters. Even at low dose, heparin administration can be associated with serious complications. Normal saline solution can maintain patency of arterial catheters and central venous pressure monitoring catheters.[1]

Arterial catheters are widely used in intensive care unit for continuous haemodynamic monitoring and frequent assessment of arterial blood gas analysis. Arterial catheters

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including radial, brachial, femoral, dorsalis pedis and axillary artery are used in the intensive care unit for continuous blood pressure monitoring, repeated blood sampling, and when there is inability to measure indirect blood pressure.[2] Invasive arterial blood pressure measurements are more accurate.[3] Flush system is used to maintain patency of arterial catheter. For this purpose, heparinized solution or normal saline should be used. Heparinized solution is used to prevent occlusion in these catheters. Heparin is an anticoagulant drug used to prevent and treat thrombosis.[4] Unfractionated heparin is a standard anticoagulant that affects multiple sites of internal and external coagulatory system and inhibits blood clotting.[5] Heparin administration can be associated with serious complications. It has a number of drug interactions, as well as potentially serious side effects. Heparin, even with low dose, can cause thrombocytopenia and bleeding.[6] The absolute risk of heparin-induced thrombocytopenia (HIT) with unfractionated heparin is 1%-5%. [7] Normal or isotonic saline has sodium and chloride concentrations of 154 mEq/L.[8] Normal saline solution can maintain patency of arterial and central venous pressure monitoring catheters. Heparinized solutions had no effect on prolonging patency and improving function of catheters and even caused changes in activated partial thromboplastin time (APTT) while the normal saline solution increases accuracy of coagulatory tests. Use of normal saline solution prevents patient exposure to the risks associated with heparinized solution and thus increase patient safety.[9]

Normal saline should be used as an alternative to heparin in arterial line and central-venous catheters. Low-dose heparin (1U/ml) should be added to the infusion set to maintain patency of arterial catheters. Extra precautionary measures must be taken when heparin therapy in instituted. Nurses and other healthcare professionals need to be reeducated on the side effects and complications of heparin therapy in order to prevent unnecessary complications and to provide safe and effective .[10]

Thrombocytopenia define as a drop in platelet count by 30% to $<100\times10^9$/l or a drop of >50% from the patient's baseline platelet count.[11] Heparin induce thrombocytopenia is defined as a decrease in platelet count during or shortly following exposure to heparin.[12] HIT is the most important and most frequent drug-induced type of thrombocytopenia. It is associated with significant morbidity and mortality if unrecognized. Despite thrombocytopenia, bleeding is rare, rather HIT is strongly associated with thromboembolic complications involving both the arterial and venous system. The risk of HIT is high with prolonged use of heparin for post-operative thromboprophylaxis. However, case studies have also demonstrate the possibility of developing HIT with minimal heparin exposure via intravascular flushes to maintain the patency of indwelling arterial or venous catheter.[13]

Methods:

This prospective randomized comparative clinical trial was conducted in the Department of Cardiac surgery, National Institute of Cardiovascular Disease (NICVD), Sher-E-Bangla Nagar, Dhaka, Bangladesh from July 2016 to June 2017. This study included sixty patients who underwent single valve replacement surgery, either MVR or AVR and shifted to the intensive care unit with arterial line catheter. The inclusion criteria for the study included 18- 60 years of age, time passed from the insertion of catheter less than 6 hours, usage of arterial line extension catheters with 20 cm, 20 gauze size, patient's blood platelet of 150000 or above, PT (Prothrombin Time) of 11-12.5 seconds, PTT (Partial Thromboplastin time) in the range of 35-45 seconds. The patients having risk of bleeding, known hypersensitivity to heparin, requiring therapeutic heparin and TPN (Total Parenteral Nutrition) during study was excluded from the study. Sampling was performed by random sampling method using random numbers generated by MS Excel software's RANDBETWEEN Function The participants were divided into two groups, one without heparin and other with heparin in normal solution. In the heparinized group, heparin (ROTEXMEDICA, TRITTAU, GERMANY) with the product number of 40124 was used. The solution was prepared by a 1000 IU of heparin added to a half liter of normal saline; hence each milliliter of the prepared solution contained 2 IU of heparin. 3 mL of the heparin solution was used for each flush. In normal saline group patients, 3 mL 0.9% sodium chloride will be used for each flush. Patients were unaware of the used method. Catheters were examined for blood return and flushing every hour using patients medical data sheets. Arterial catheter was remain upto 72 hours. During the examination of catheters, all patients were lying on their backs. If flushing or taking blood sample from the catheter was not possible, it was considered non-functional and removed. Platelet count was measured manually preoperative, post pump and daily for 4 postoperative days then on 7^{th} and 14^{th} postoperative days. The maximum time of study was 14th days and the collected data during the first 4 days were recorded every four hours in the previously prepared checklist. At the end of 1^{st} week and 2^{nd} week platelet count were recoded and whole data were analyzed by SPSS software version 23. In this study for describing the features of research units, descriptive statistics (mean, standard deviation and distribution frequency) was used. For analyzing the data, Kaplan Meier survival analysis, log rank test and Cox regression was performed and for comparing the ratios, the Chi-square test was used. $p < 0.05$ was considered significant.

The statistical package for the social science program (SPSS-22.0 Inc) was used to evaluate all data. The tests statistics were used to analyze the data are student's t test. The qualitative data were presented as frequency with

corresponding percentage. For all analytic test s, the level of significance was set at 0.05 and a p value of <0.05 was considered significant. The summarized data were presented in the form of tables and charts.

Results:

Table-1 shows that patients maximum patients within 31-40 years in both groups. The mean age of Group-A was 36.3 yrs and that of Group –B was 35.7±10.3 years. The mean difference between the two groups was not statistically significant.

Table-I

Distribution of patients by age (n=60)

Age (years)	Group		p value
	Group-A (n=30)	Group-B (n=30)	
	No. (%)	No. (%)	
< 20	0(0.0%)	3(10.0%)	
21-30	7(23.3%)	5(16.7%)	
31-40	13(43.3%)	13(43.3%)	
41-50	10(33.3%)	6(20.0%)	
51-60	0(0.0%)	3(10.0%)	
Total	30(100.0%)	30(100.0%)	
Mean±SD	36.3±6.7	35.7±10.3	0.790^{ns}

Group-A: Heparinized flush solution group
Group-B: Normal saline group
Data were analysed using Student's t-test and were presented as mean ± SD

Table-II shows that females were predominant in both Group. 60.0% patients were female in Group A and 63.3% in Group B. There is no significant difference between the groups in respect to sex (p = 0.790).

Table-II

Comparison of patients by sex between Group-I and Group-II

Genders	Group		p value
	Group-A (n=30) No. (%)	Group-B (n=30) No. (%)	
Male	12(40.0%)	11(36.7%)	0.790
Female	18(60.0%)	19 (63.3%)	
Total	30(100.0%)	30(100.0%)	

Group-A: Heparinized flush solution group
Group-B: Normal saline group
Chi square test was done to analyze the Data. Degree of freedom (df) =1
Figure in the parenthesis denoted corresponding percentage.

Name of operation

Table-III shows type of operation, maximum 73.3% cases had MVR in Group A and 56.7% in Group B. AVR were 26.7% in Group A and 43.3% in Group B. No significant difference between two groups.

Table-III

Distribution of the study by name of operation

Name of operation	Group		p value
	Group-A (n=30) No. (%)	Group-B (n=30) No. (%)	
MVR	22(73.3%)	17(56.7%)	0.175
AVR	8(26.7%)	13 (43.3%)	
Total	30(100.0%)	30(100.0%)	

Group-A: Heparinized flush solution group
Group-B: Normal saline group
Chi square test was done to analyze the Data. Degree of freedom (df) =1
Figure in the parenthesis denoted corresponding percentage.

Platelet count

Table-IV showed comparison of platelet count between two groups. There is no statistically significant difference

Table-IV

Comparison of platelet count in two groups in different POD.

Platelet count	Group-A (n=30)Mean±SD	Group-B (n=30)Mean±SD	P value
Pletelet count pre operative	247583±55675	235813±54708	0.412 ^{ns}
Pletelet count post pump	215883±58210	222580±52422	0.633 ^{ns}
Pletelet count 1st POD	206530±64441	212543±48768	0.685 ^{ns}
Pletelet count 2nd POD	208363±58003	222177±55580	0.350 ^{ns}
Pletelet count 3rd POD	226517±60185	245957±52826	0.188 ^{ns}
Pletelet count 4th POD	241217±57558	258190±55012	0.247 ^{ns}
Pletelet count 7th POD	240517±57379	257713±53655	0.236 ^{ns}
Pletelet count 14th POD	245850±52680	244337±56796	0.915^{ns}

Group-A: Heparinized flush solution group
Group-B: Normal saline group
Data were analysed using Student's t-test and were presented as mean ± SD

between Group A and Group B at preoperative period, post pump, 1st POD, 2nd POD, 3rd POD, 4th POD, 7th POD and 14th POD (p >0.05).

Arterial line

Table-V shows arterial line patency in study patients. 100% patients had arterial line patent in 1st POD in both groups. In 2nd POD 86.8% patients had patency in Group A and 76.7% in Group B. At 3rd POD 50.0% patients had patency in Group A and 43.3% patients in Group B. No significant difference between two groups (p> 0.05).

Table-V

Distribution of the study by arterial line

Arterial line	Group		p value
	Group-A (n=30) No. (%)	Group-B (n=30) No. (%)	
1st POD	30(100.0%)	30(100.0%)	1.000 ns
2nd POD	26(86.7%)	23 (76.7%)	0.316 ns
3rd POD	15(50.0%)	13(43.3%)	0.607ns

Group-A: Heparinized flush solution group
Group-B: Normal saline group
Chi square test was done to analyze the Data. Figure in the parenthesis denoted corresponding percentage.

Hospital stay and ICU stay

Table showed that mean hospital stay and ICU stay were not significant difference between Group A and Group B (p>0.05).

Table-VI

Comparison of hospital stay between two groups

Hospital stay	Group-A (n=30) Mean±SD	Group-B (n=30) Mean±SD	p-value
Hospital stay	11.41±3.12	12.14±3.69	0.411ns
ICU stay	5.63±2.23	4.64±2.47	0.108ns

Group-A: Heparinized flush solution group
Group-B: Normal saline group
Data were analysed using Student's t-test and were presented as mean ± SD

Discussion:

This study found no statistically significant difference between heparinized flush solution group and normal saline group at preoperative period, post pump, 1st POD, 2nd POD, 3rd POD, 4th POD, 7th POD and 14th POD (p >0.05) on platelet counts. Over time for individual patients who had arterial lines for 4 days or longer, Counts showed an early decline and then recovery to normal levels in both the heparinized and normal saline groups. The parallel study done by Hall *et al* comparing arterial catheter line in the two groups showed no difference at the 95% confidence interval using the central limit theorem.[14] Sixty-five patients were recruited over 8 months: 35 in the normal saline group and 30 in the heparinized saline group. The mean platelet count was 256.6×10^9/L for the heparinized saline group, compared with 234.6×10^9/L for the normal saline group. Comparison of means with the central limit theorem showed there was no significant difference at the 95% confidence interval.

In 1991, Clifton conducted a double-blind, randomized study comparing the effects of heparin solutions (4 IU/mL) and normal saline solutions on patency of arterial catheters. They concluded that heparinised solutions were preferable for reducing the rate of catheter occlusions and other malfunctions and that they did not significantly alter platelet count. However, their study included only 30 patients, and patients were excluded from the study if baseline platelet counts were below 50×10^9/L.[15]

Another study of 35 ICU patients compared use of either heparin (4 IU/mL) or 1.4% sodium citrate, both in 0.9% sodium chloride solution, as a continuous flush solution. Again, platelet counts were similar in the two groups.[16]

The results of the current study showed no statistically significant difference regarding the patients' demographic characteristics such as age and gender between heparinized flush solution group and normal saline group. The most common site of arterial catheters similar to those of the previous studies was radial artery. The proportion of arterial catheters placement sites including radial, brachial and femoral arteries were similar to those of the previous studies and there was no statistically significant difference between the two groups.[17]

In present showed arterial line patency, 100% patients had arterial line patent in 1st POD in both groups. In 2nd POD 86.8% patients had patency in Group A and 76.7% in Group B. At 3rd POD 50.0% patients had patency in Group A and 43.3% patients in Group B. No significant difference between two groups (p> 0.05). It is Similar to those of the previous studies.[17] In a current systematic review study Kordzadeh *et al* determined that, heparinized saline solution may be superior for long term use in arterial line.[18] However the current study assessed this issue in short term period and found no significant difference. Cardiac valve surgery and in the current study there was no statistically significant difference between the two groups, but in the other studies were not surveyed. Variable alteration during three days of patients follow up including catheters patency and other parameters did not significantly change that was similar to the obtained results of the studies in which patients were followed up from several days to 12 months.[17,6,19] Based on the finding of the current double blind randomized clinical

trial, use of heparinized saline solutions compared with normal saline solutions did not prolong the patency of arterial and central venous catheters in short term postoperative period. Finding of the study suggested that normal saline solution can be used as the standard solution to prevent catheter occlusion after cardiac surgery. Therefore, all medical centers are suggested to prevent heparin complications such as allergic reaction, local tissue injury, bleeding, thrombus and thrombocytopenia related to use of heparin in patients with arterial and central venous catheter; normal saline solution can be used to prevent catheter patency as a safe alternative solution.

It seems that the use of heparinized saline and normal saline solution in preventing patency of arterial line has no difference. Our finding only applicable to cardiac valve surgery patients that have arterial line catheters for short time period (3 three days) post-operatively. Therefore these data could not be generalizable to chronic medical situations.

A randomized, double-blind, placebo-controlled trial by Del Cotillo et al. concluded that use of heparinized solutions did not increase catheter patency.[17] Hall et al. found a similar conclusion that heparin as a continuous flush at 3U/ml did not improve the function of arterial lines as compared with saline flush.[14] Leighton concludes that it is practical to maintain arterial lines with normal saline as it has the same benefit as heparin without the risks associated with heparin.[20] However, Clifton *et al.* contradicts the conclusion that normal saline is beneficial.[15] Their study states that use of normal saline as a continuous flush for radial artery catheters is associated with increased frequency of catheter occlusions compared with heparin.

Lapum et al. were neutral in their results and concluded that no significant differences were found between intravascular catheters flushed with heparinized solution and those flushed with nonheparinized solutions.[21,4,22] Majority of the studies mentioned above used heparin at varying doses (0.25 U/mL or 1U/mL). Studies done to determine the effective dose of heparin conclude that 0.25 U/mL is sufficient for maintenance of arterial catheters.[23] Majority of the available data suggest that heparin saline given as a continuous flush at low doses improved catheter patency. However, heparin as an intermittent flush is ineffective.

Limitation:

Arterial catheter patency was assessed only for three postoperative days. so, findings regarding prolonged maintenance of indwelling catheters by heparinized or normal saline solutions were not representative. It would be better to have large sample size to predict patency rate of indwelling arterial catheter.

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